Articles

Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack

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Summary

Background Blood pressure is a determinant of the risk of stroke among both hypertensive and non-hypertensive individuals with cerebrovascular disease. However, there is uncertainty about the efficacy and safety of blood-pressure-lowering treatments for many such patients. The perindopril protection against recurrent stroke study (PROGRESS) was designed to determine the effects of a blood-pressure-lowering regimen in hypertensive and non-hypertensive patients with a history of stroke or transient ischaemic attack.

Methods 6105 individuals from 172 centres in Asia, Australasia, and Europe were randomly assigned active treatment (n=3051) or placebo (n=3054). Active treatment comprised a flexible regimen based on the angiotensin-converting-enzyme inhibitor perindopril (4 mg daily), with the addition of the diuretic indapamide at the discretion of treating physicians. The primary outcome was total stroke (fatal or non-fatal). Analysis was by intention to treat.

Findings Over 4 years of follow up, active treatment reduced blood pressure by 9/4 mm Hg. 307 (10%) individuals assigned active treatment suffered a stroke, compared with 420 (14%) assigned placebo (relative risk reduction 28% [95% CI 17–38], p<0·0001). Active treatment also reduced the risk of total major vascular events (26% [16–34]). There were similar reductions in the risk of stroke in hypertensive and non-hypertensive subgroups (all p<0·01). Combination therapy with perindopril plus indapamide reduced blood pressure by 12/5 mm Hg and stroke risk by 43% (30–54). Single-drug therapy reduced blood pressure by 5/3 mm Hg and produced no discernable reduction in the risk of stroke.

Interpretation This blood-pressure-lowering regimen reduced the risk of stroke among both hypertensive and non-hypertensive individuals with a history of stroke or transient ischaemic attack. Combination therapy with perindopril and indapamide produced larger blood pressure reductions and larger risk reductions than did single drug therapy with perindopril alone. Treatment with these two agents should now be considered routinely for patients with a history of stroke or transient ischaemic attack, irrespective of their blood pressure.

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Introduction

Strokes kill about 5 million people each year, making cerebrovascular disease the second leading cause of death worldwide.[1] At least 15 million others have non-fatal strokes annually, and about a third are disabled as a consequence.[2,3] Among those who survive a stroke or a transient ischaemic attack, the risk of further stroke is very high: at least one in six suffer another stroke within 5 years.[3] The identification of safe and effective treatments for the prevention of recurrent stroke is therefore a priority. Antiplatelet therapy reduces the risk of stroke and other major vascular events by between a sixth and a fifth among individuals with a history of ischaemic stroke or transient ischaemic attack,[4,5] and is now prescribed routinely to these patients. Carotid endarterectomy reduces the risk of recurrent ipsilateral stroke in those with carotid stenosis,[6,7] and anticoagulant therapy reduces recurrent stroke risk in those with atrial fibrillation,[8] but each of these two treatments is suitable for only a small proportion of all patients with ischaemic stroke or transient ischaemic attack. No treatment has been proven to reduce recurrent stroke risk among patients with a history of cerebral haemorrhage.

Observational studies have shown that usual blood pressure levels are directly and continuously associated with the initial occurrence of ischaemic stroke and cerebral haemorrhage.[9] As a consequence, blood pressure is recognised as an important determinant of the risk of initial stroke in non-hypertensive individuals as well as in those with hypertension.[9,10] Fewer data are available about the associations of blood pressure with recurrent stroke. Hypertension has been associated with an increased risk of stroke recurrence in some,[11,12] but not other,[13] community studies of outcome after first stroke. In two small clinical studies,[14,15] blood pressure seemed to be directly associated with the risk of stroke recurrence among patients with a history of recent cerebral haemorrhage. In one of these studies,[14] a J-shaped relation between blood pressure and recurrent stroke was seen among patients with a recent history of ischaemic stroke. However, such non-linearity might reflect "reverse causality", whereby the most severe cerebrovascular disease lowers blood pressure and independently worsens prognosis.[16] A much larger study[17] of 2435 clinically stable individuals with a history of minor ischaemic stroke or transient ischaemic attack detected no evidence of non-linearity in the association of usual blood pressure with stroke recurrence: each 10 mm Hg lower level of systolic pressure was associated with a 28% (SE 8) lower risk of stroke.

Systematic reviews of randomised trials of blood-pressure-lowering drugs in hypertensive patients, mostly without cerebrovascular disease, have shown that sustained blood pressure reductions of about

5–6 mm Hg diastolic reduced the risk of initial stroke by about a third,[18] with no large differences apparent between the main drug classes.[19] Those studies provided little evidence about the separate effects of treatment on ischaemic stroke and cerebral haemorrhage. There are comparatively few randomised trials of blood-pressure-lowering drugs among patients with a history of cerebrovascular disease: a meta-analysis[20] of the four trials with published final results (involving 2742 patients, most of whom had a history of ischaemic stroke) suggested that blood pressure reductions of about 6–8 mm Hg systolic and 3–4 mm Hg diastolic were associated with a fifth fewer recurrent strokes. However, the confidence interval for this estimate of treatment effect was wide and consistent with no worthwhile effect as well as with benefit. Analyses of subsets of patients with a history of cerebrovascular disease included in other trials of antihypertensive treatment regimens[21] or of angiotensin-converting-enzyme (ACE) inhibitors[22] yielded similar results. Clearer evidence of benefits of blood-pressure-lowering treatments for recurrent stroke risk was provided by a preliminary report from a trial of the diuretic indapamide among 5665 individuals with previous stroke or transient ischaemic attack.[23] However, final results from that study remain unpublished.

The perindopril protection against recurrent stroke study (PROGRESS)[24] was started by an independent collaborative research group in an effort to resolve clinical uncertainty about the efficacy and safety of routine blood-pressure-lowering therapy for individuals with a history of stroke or transient ischaemic attack. We report here the principal results from this randomised, placebo-controlled trial.

Patients and methods

The aim of PROGRESS was to determine the effects of a flexible blood-pressure-lowering regimen, involving an ACE inhibitor (perindopril) and a diuretic (indapamide), on the risk of stroke and other major vascular events among individuals with a history of stroke or transient ischaemic attack. The study was conducted in 172 collaborating centres from ten countries (see end of paper). The institutional ethics committee of each collaborating centre approved the trial and all participants provided written informed consent. The study methods and objectives are published in detail elsewhere[24] and are described here in brief.

Patients

Patients were potentially eligible if they had a history of stroke (evidence of an acute disturbance of focal neurological function with symptoms lasting more than 24 h and thought to be due to intracerebral haemorrhage or ischaemia) or transient ischaemic attack (evidence of an acute disturbance of focal neurological or monocular function with symptoms lasting less than 24 h and thought to be due to arterioembolic or thrombotic vascular disease) within the previous 5 years. Participants were required to have, in the opinion of the responsible physician, no definite indication (such as heart failure) for treatment with an ACE inhibitor and no definite contraindication (such as previous intolerance) to such treatment. There were no blood pressure entry criteria, although it was recommended that individuals with uncontrolled hypertension receive antihypertensive therapy with agents other than ACE inhibitors before entry to the trial. It was also recommended that participants should be clinically stable for at least 2 weeks after their most recent vascular event before entry to the study.

Methods

Potentially eligible individuals entered a 4-week prerandomisation run-in period during which they received open-label perindopril (2 mg daily for 2 weeks, followed by 4 mg daily for another 2 weeks). Participants who adhered to, and tolerated, the run-in treatment were randomly assigned, on a double-blind basis, continued active therapy or matching placebo. Active treatment comprised a flexible regimen based on perindopril (4 mg daily) with the addition of indapamide (2·5 mg daily, except in Japan where the dose was 2·0 mg daily) in patients for whom the responsible physician judged there to be no specific indication for or contraindication to treatment with a diuretic. Patients assigned placebo received placebo tablets identical in appearance to perindopril, and those for whom the attending physician judged there to be no specific indication for or contraindication to treatment with a diuretic also received placebo tablets identical in appearance to indapamide. The rationale for allowing the use of combination therapy was to maximise the size of the blood pressure reduction achieved.

Flexibility with regard to the use of combination or single-drug therapy (or matching placebos) for individual patients was an important clinical consideration, given the initial uncertainty of many collaborating doctors about the safety of intensive blood-pressure lowering for patients with cerebrovascular disease, particularly those with ischaemic stroke or transient ischaemic attack, and average, or below average, blood pressure at entry. Similar considerations have guided the use of study treatment regimens in many other blood-pressure-lowering trials,[18,19] in which the treating physicians were given some discretion as to the intensity of treatment provided to individual patients. However, in the present study, unlike most previous trials, the responsible physician was asked before randomisation about his or her intentions with respect to treatment intensity. Thus, the randomised treatment allocation in PROGRESS could be stratified by the intention to use a single study tablet (perindopril or single placebo) or combination study tablets (perindopril plus indapamide, or double placebo), as well as by study centre, age, sex, entry systolic blood pressure, and qualifying event. Study treatment allocation was provided by a central computer-based randomisation service accessed by telephone or facsimile. Participants were instructed to take study tablets daily. All other aspects of medical and surgical care were left to the discretion of the responsible physician.

In the year after randomisation, participants were seen on five occasions. In the second and subsequent years, visits were held every 6 months. At these visits, the data collected included information on adherence to study treatments, tolerability of study treatments, blood pressure, cognitive function, disability, and the occurrence of major clinical events. Blood pressure was measured in duplicate, to the nearest 2 mm Hg, with a standard mercury sphygmomanometer. Wherever possible, clinic visits were continued for the entire scheduled duration of follow-up for all surviving randomised participants, including those who discontinued study drug treatment for any reason.

The primary study outcome was fatal or non-fatal stroke, defined as an acute disturbance of focal neurological function with symptoms lasting more than 24 h (or resulting in earlier death), and thought to be due to either cerebral infarction or cerebral haemorrhage. Secondary outcomes included: fatal or disabling stroke

with disability defined at the first scheduled follow-up visit after the event by a positive response to the question "in the past 2 weeks has the patient required regular help with everyday activities?";[25] total major vascular events comprising the composite of non-fatal stroke, non-fatal myocardial infarction, or death due to any vascular cause (including unexplained sudden death); total and cause-specific deaths; and hospital admissions. Data on other secondary outcomes, including dementia and cognitive function, will be reported elsewhere.

An endpoint adjudication committee reviewed source documentation for all individuals who had a suspected stroke or myocardial infarction or who died during the scheduled period of follow-up. Outcomes were coded according to the ninth revision of the International Classification of Diseases, and strokes were subclassified as cerebral haemorrhage, ischaemic stroke, or stroke of unknown pathological type. A stroke or myocardial infarction was classified as non-fatal if the patient was alive 28 days after the onset of the event. An independent data monitoring committee reviewed unmasked outcome data about once a year throughout follow-up. That committee's brief was to inform the study investigators if at any time there emerged evidence beyond reasonable doubt of a difference between randomised groups in survival, and evidence that was likely to materially alter the management of patients with a history of stroke or transient ischaemic attack.

Statistical analysis

The planned study sample size (6000 participants) and average follow-up duration (4 years) was calculated assuming an annual stroke rate among control patients of between 1·5 and 2·0%, an average difference in diastolic blood pressure between active treatment and placebo groups of 4 mm Hg, and (by inference from the projected blood pressure difference) a reduction of 30% in total stroke risk among those assigned active treatment. On this basis, it was estimated that the study would have at least 90% power to detect the expected effects of treatment on stroke (with α=0·05 and equal sample sizes in the two randomised groups).

In all analyses, participants were grouped according to their original randomised treatment allocation (ie, by the principle of intention to treat), irrespective of whether treatment was continued for the entire duration of follow-up. Differences in tolerability were assessed from χ^2 tests comparing the proportions permanently withdrawn from all study drugs or placebos before the scheduled end of follow-up or prior death. Differences in blood pressure between randomised groups during follow-up were estimated by use of linear mixed models. Cumulative event curves were estimated with the Kaplan-Meier procedure, and the effects of treatment on the primary and secondary endpoints were estimated from unadjusted Cox's proportional hazards models. Among participants who had more than one outcome event during follow-up, survival time to the first relevant event was used in each analysis. If a participant had more than one type of event (eg, an ischaemic stroke and a haemorrhagic stroke), each event would contribute to the relevant cause-specific analysis, but only one event from any individual (the first, if more than one) contributed to any single analysis (eg, total stroke). Participants who died from other causes were treated as censored. Relative risk reductions are described in the text and figures as percentage reductions ([1−hazard ratio]×100). All p values were calculated from two-tailed tests of statistical significance.

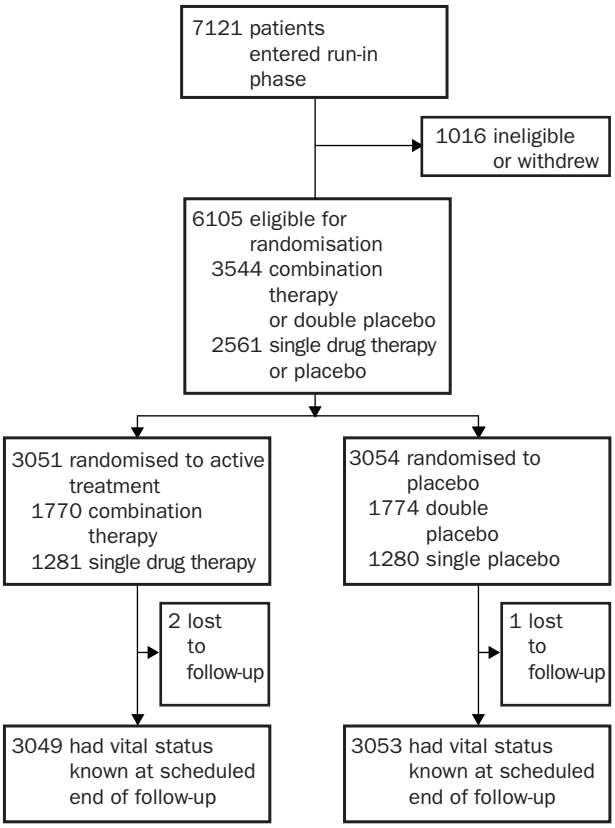


Figure 1: **Trial profile**

Two subgroup analyses were prespecified in the statistical analysis plan: separate estimates of treatment effects among participants for whom combination therapy was planned at randomisation and those for whom single drug therapy was planned; and separate estimates of treatment effects among participants classified as hypertensive (systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg at baseline, irrespective of any use of antihypertensive treatment) and those classified as non-hypertensive at entry to the study. The definition of hypertension used in these analyses was based on the lowest levels of blood pressure adopted as entry criteria in earlier trials in which antihypertensive treatment regimens were shown to reduce stroke risks.[18,19] Standardised estimates of treatment effects in hypertensive and non-hypertensive participants were calculated by combining subgroup-specific estimates of the effects of combination therapy and of single-drug therapy, with each component weighted by the study-wide proportion for which combination therapy (58%) or single-drug therapy (42%) was planned at entry. Homogeneity of treatment effects between subgroups was tested by adding interaction terms to the relevant statistical models.

Results

Patients' enrolment and baseline characteristics

7121 potential participants were registered and 1016 (14%) were subsequently found to be ineligible or withdrew during the 4-week active run-in period (figure 1). The main reasons for withdrawal during this period were dizziness or hypotension (3·4%), cough (2·7%), other suspected intolerance (2·3%), and participant's decision (2·0%). One case of non-fatal angio-oedema was documented during the run-in phase. 6105 individuals

Characteristic	Randomised treatment		Prespecified regimen*	
	Active (n=3051)	Placebo (n=3054)	Combination (active or placebo; n=3544)	Single (active or placebo; n=2561)
Demographics				
Mean (SD) age (years)	64 (10)	64 (10)	63 (9)	65 (10)
Number of women	923 (30%)	929 (30%)	1043 (29%)	809 (32%)
Number Asian†	1176 (39%)	1176 (39%)	1357 (38%)	995 (39%)
Cerebrovascular disease history				
Number with previous stroke				
Ischaemic stroke	2157 (71%)	2153 (71%)	2520 (71%)	1790 (70%)
Cerebral haemorrhage	332 (11%)	328 (11%)	387 (11%)	273 (11%)
Unknown stroke	134 (4%)	148 (5%)	141 (4%)	141 (6%)
TIA or amaurosis fugax	681 (22%)	689 (22%)	771 (22%)	591 (23%)
Median (IQR) time since qualifying event (months)	8 (2–21)	8 (2–22)	7 (2–21)	9 (3–23)
Other medical history				
Current smoker	606 (20%)	614 (20%)	721 (20%)	499 (19%)
Diabetes	394 (13%)	368 (12%)	425 (12%)	337 (13%)
Coronary heart disease	493 (16%)	490 (16%)	636 (18%)	347 (14%)
Blood pressure and hypertension status				
Mean (SD) systolic blood pressure (mm Hg)	147 (19)	147 (19)	149 (19)	144 (19)
Mean (SD) diastolic blood pressure (mm Hg)	86 (11)	86 (11)	87 (11)	84 (11)
Hypertension‡	1464 (48%)	1452 (48%)	1903 (54%)	1013 (40%)
Antihypertensive therapy	1510 (50%)	1554 (51%)	1764 (50%)	1300 (51%)

TIA=transient ischaemic attack. *Combination=perindopril plus indapamide, or double placebo; single=perindopril alone or single placebo. †Participants recruited from China or Japan. ‡Systolic blood pressure ⩾160 mm Hg or diastolic blood pressure ⩾90 mm Hg.

Baseline characteristics of randomised participants

entered the randomised, double-blind phase: 3051 were assigned active treatment and 3054 were assigned placebo. Of those assigned active treatment, the regimen comprised combination therapy with perindopril plus indapamide for 1770 individuals (58%) and single-drug therapy with perindopril alone for 1281 (42%). Of those assigned placebo, the regimen comprised double placebo for 1774 individuals (58%) and single placebo for 1280 (42%).

The characteristics of randomised participants are described in detail elsewhere[26] and are summarised in the table. There was good balance between active treatment and placebo groups for all recorded participant characteristics. 2916 (48%) participants were classified as hypertensive on the basis of blood pressure readings made at the first visit. At that visit, the mean blood pressure of all participants was 147/86 mm Hg: among those classified as hypertensive, the mean was 159/94 mm Hg and among those classified as non-hypertensive it was 136/79 mm Hg. There was also good balance of baseline characteristics between active treatment and placebo groups within the combination therapy or double placebo and single-drug therapy or single placebo subgroups. However, those for whom combination therapy or double placebo was planned tended to be younger, were more likely to be men, had higher blood pressures at entry, were more likely to be hypertensive, were more likely to have coronary heart disease, and were recruited sooner after their qualifying cerebrovascular event than those for whom single-drug therapy or single placebo was intended.

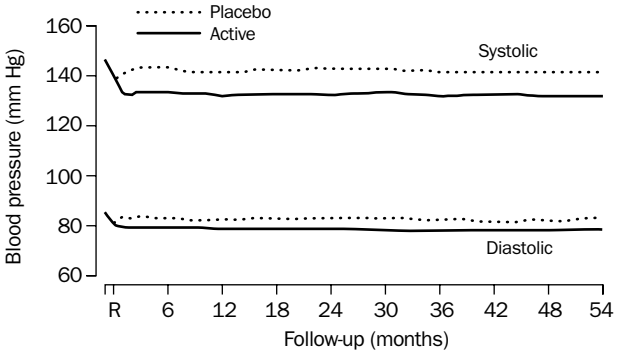


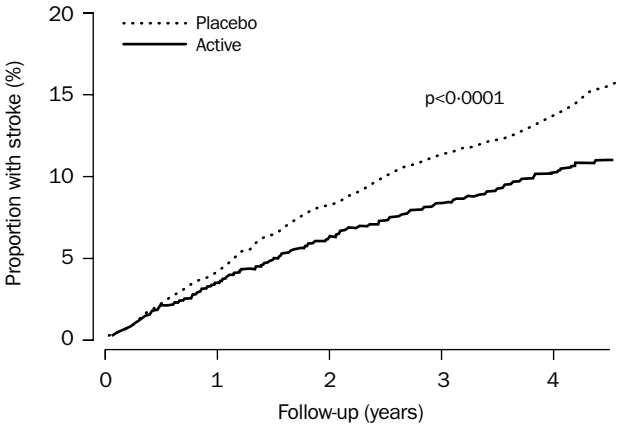
Figure 2: **Changes in systolic and diastolic blood pressure among participants assigned active treatment and those assigned placebo**
R=randomisation visit.

Duration of follow-up and adherence to study treatment

The mean duration of follow-up was 3·9 years (11 893 patient-years among those assigned active treatment and 11 889 patient-years among those assigned placebo), representing an average of 4·1 years among those who survived to the scheduled end of follow-up and 2·3 years among those who died during follow-up. Randomised therapy was continued for 10 196 patient-years (86%) among those assigned active treatment and 10 392 patient-years (87%) among those assigned placebo. By the end of scheduled follow-up, or death before that time, 1350 (22%) participants had prematurely discontinued all study tablets (active 714 [23%], placebo 636 [21%]; p=0·02). The main reasons for discontinuation were participant's decision (active 232 [7·6%], placebo 250 [8·2%]), cough (active 47 [2·2%], placebo 69 [0·4%]), hypotension (active 64 [2·1%], placebo 29 [0·9%]), and heart failure requiring treatment with an ACE inhibitor or diuretic (active 47 [2·2%], placebo 69 [2·3%]). The rates of discontinuation were broadly similar among participants classified as hypertensive (active 320 [22%], placebo 315 [22%]) and those classified as non-hypertensive (394 [25%] active, 321 [20%] placebo). Three cases of angio-oedema were documented among those treated with perindopril during double-blind follow-up; none were fatal or required intubation.

Effects on blood pressure

Blood pressure (systolic/diastolic) was reduced by an overall average of 9·0/4·0 mm Hg (SE 0·3/0·2) among those assigned active treatment compared with those assigned placebo. These differences were maintained throughout follow-up, with no evidence of attenuation (figure 2). Compared with those assigned placebo, the blood pressure reductions among those treated with combination therapy (12·3/5·0 mm Hg [0·5/0·3]) were about twice as great as those among participants treated with single-drug therapy (4·9/2·8 mm Hg [0·6/0·3]).



Numbers at risk

Active	3051	2902	2765	2634	1595
Placebo	3054	2880	2707	2551	1533

Figure 3: **Cumulative incidence of stroke among participants assigned active treatment and those assigned placebo**

There were only small differences between the standardised blood pressure reductions seen among participants classified as hypertensive (9·5/3·9 mm Hg [0·6/0·3]) and those classified as non-hypertensive at entry (8·8/4·2 mm Hg [0·5/0·3]).

Effects on stroke

727 participants had a stroke during follow-up: 307 (10%) in the active group and 420 (14%) in the placebo group (relative risk reduction 28% [95% CI 17–38%]; p<0·0001). The cumulative stroke curves diverged early and continued to separate throughout follow-up (figure 3). The annual rate of new cases of stroke was 2·7% in the treatment group and 3·8% in the control group. There was no clear evidence of heterogeneity in the size of the hazard ratios between subgroups of participants defined by type of qualifying cerebrovascular event (haemorrhagic or ischaemic), time between the qualifying event and enrolment (<6 months or 6 months–5 years), or geographic region of residence (Asia or elsewhere; p for homogeneity all >0·1).

Overall, 92 (13%) strokes were fatal and a further 212 (29%) were non-fatal but disabling. Fewer patients in the active group than the placebo group had strokes that were fatal or disabling, and fewer in the active group had less severe strokes (figure 4). Overall, 565 participants were judged to have had an ischaemic stroke during follow-up, 111 a cerebral haemorrhage and 93 a stroke of unknown pathological type. Again, fewer patients in the active group than the placebo group had either ischaemic stroke or cerebral haemorrhage (figure 4).

Effects on major vascular events

During follow-up, 1062 participants had a major vascular event (379 fatal events and 683 major non-fatal events): 458 (15%) in the active treatment group and 604 (20%) in the placebo group (figure 4). The annual rate of new cases was 4·1% in the treatment group and 5·5% in the control group. Fewer patients in the active group than the placebo group had non-fatal stroke or non-fatal myocardial infarction; however, there was no difference between the groups in terms of vascular death (figure 4). There were fewer total major coronary events (non-fatal myocardial infarction or death from coronary heart disease) among participants assigned active treatment (115) than among those on placebo (154; relative risk reduction 26% [95% CI 6–42]).

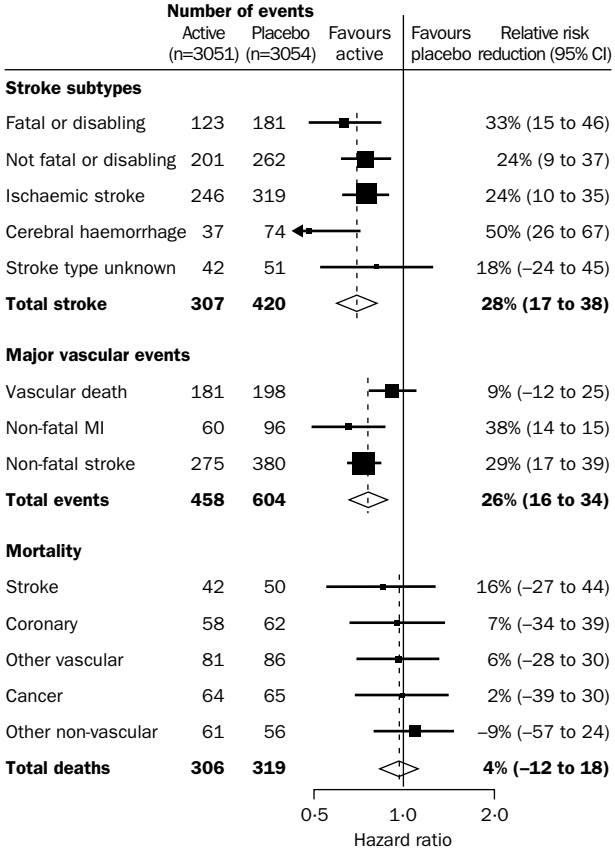


Figure 4: **Effects of study treatment on stroke subtypes, major vascular events, and deaths**

Black squares=point estimates (with area proportional to number of events); horizontal lines=95% CIs. Diamonds=point estimate and 95% CI for overall effects. Vertical broken line=point estimate for overall effect. MI=myocardial infarction.

Effects on deaths and hospital admissions

Data on vital status at the scheduled end of follow-up were available for all but three (0·05%) randomised participants. 625 individuals died during the study (379 from vascular causes and 246 from non-vascular causes). There were no significant differences between randomised groups in total deaths or deaths from vascular or non-vascular causes (figure 4). 2601 participants were admitted to hospital on 5085 occasions during follow-up. Among those assigned active treatment, there was a reduction in the proportion of participants admitted to hospital during the scheduled follow-up period (1252 [41%] *vs* 1349 [44%], relative risk reduction 9% [95% CI 1–15]), with a median reduction of 2·5 days in the time spent in hospital during follow-up.

Effects of combination and single-drug therapy

Among participants treated with the combination of perindopril plus indapamide (in whom blood pressure was lowered by a mean of 12/5 mm Hg), stroke risk was significantly lower than that among participants who received double placebo (figure 5). Among participants treated with perindopril alone (in whom blood pressure was lowered by a mean of 5/3 mm Hg), stroke risk was not discernibly different from that among participants who received single placebo (figure 5). There was significant heterogeneity in the sizes of these treatment effects (p for homogeneity <0·001). Neither the strength of this evidence of heterogeneity nor the individual hazard ratios were materially affected by statistical

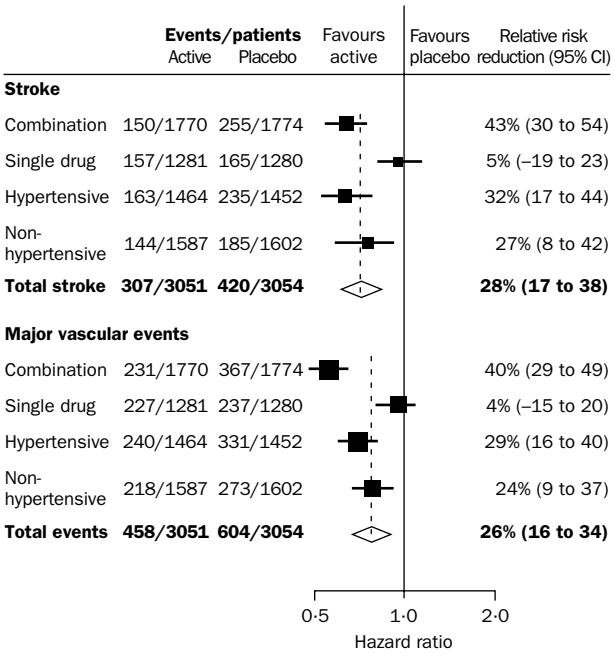


Figure 5: **Effects of study treatment on stroke and major vascular events in subgroups of patients**

Hazard ratios (and 95% CIs) for hypertensive and non-hypertensive subgroups standardised to study-wide proportions of patients for whom combination or single drug therapy was planned. p values for homogeneity (combination therapy *vs* single drug therapy) both <0·001. p values for homogeneity (hypertensive *vs* non-hypertensive) both >0·6. Conventions as in figure 4.

adjustment for the characteristics listed in the table. In comparison with double placebo, combination therapy was associated with a lower risk of each of the main stroke subtypes: fatal or disabling stroke (60/1770 *vs* 110/1774; 46% [95% CI 27–61]), ischaemic stroke (126 *vs* 191; 36% [19–49]), and cerebral haemorrhage (12 *vs* 49; 76% [55–87]).

Among participants treated with combination therapy, the risk of any major vascular event was lower than that among patients who received double placebo (figure 5). The risk of the same outcome among participants treated with single drug therapy was, once again, not discernibly different from that among those who received single placebo (figure 5). There was significant heterogeneity in the sizes of these treatment effects (p for homogeneity <0·001). Combination therapy was associated with fewer cases of each component of this composite outcome than double placebo: non-fatal stroke (138 *vs* 232; 42% [29–53]), non-fatal myocardial infarction (34 *vs* 58; 42% [11–62]), and vascular death (88 *vs* 121; 28% [5–45]). Compared with double placebo, combination therapy was also associated with fewer total major coronary events (67 *vs* 102: 35% [12–52]).

Effects in hypertensive and non-hypertensive participants

The standardised reductions in stroke risk were of similar size in hypertensive and non-hypertensive participants (p for homogeneity=0·7, figure 5). The reductions in the risk of major vascular events were also similar in these two groups of patients (p for homogeneity=0·6, figure 5). Combination therapy seemed to confer similar advantages over single-drug therapy for both hypertensive and non-hypertensive participants: the reduction in stroke risk with combination therapy was 44% (95% CI 28–57) among hypertensive individuals (93/948 *vs* 159/955) and 42% (19–58) among non-hypertensive individuals (57/822 *vs* 96/819), whereas the reductions with single-drug therapy were 10% (−25 to 35) among hypertensives (70 *vs* 76) and 1% (−34 to 26) among non-hypertensives (87 *vs* 89).

Discussion

This randomised controlled trial among individuals with previous stroke or transient ischaemic attack shows that a flexible blood-pressure-lowering regimen, which included perindopril for all patients and indapamide for 58%, reduced blood pressure by an average of 9/4 mm Hg and the risk of stroke by more than a quarter. Over 4 years, annual stroke incidence was reduced from 3·8% to 2·7%. There was a reduction in the risk of fatal or disabling stroke as well as that of less severe stroke, and a reduction in the risk of ischaemic stroke as well as that of cerebral haemorrhage. Importantly, stroke risk was reduced not only among participants classified as hypertensive but also among those classified as non-hypertensive, among whom mean blood pressure at entry was 136/79 mm Hg. The relative risk reductions seemed to be of broadly similar size among participants with a history of ischaemic or haemorrhagic cerebrovascular disease, among those recruited early or late after their last cerebrovascular event, and among those recruited from Eastern or Western populations. In addition to the reduction in stroke risk, there was a reduction of about a quarter in the risk of major coronary events and a similar reduction in total major vascular events.

These benefits were achieved against a background of standard care that included antiplatelet therapy for most of those with previous ischaemic stroke or transient ischaemic attack, and non-study antihypertensive drug therapy for half of all participants. The benefits were also achieved in the context of a low withdrawal rate for adverse effects: after initial screening for intolerance of perindopril during the run-in phase, there was only 2% more withdrawals from active therapy than placebo after 4 years of double-blind follow-up. These results should, therefore, resolve much of the clinical uncertainty that has existed about the benefits and safety of blood-pressure-lowering treatments for patients with a history of stroke (whether ischaemic or haemorrhagic) or of transient ischaemic attack. Moreover, the evidence of benefits for non-hypertensive participants, as well as for those with hypertension, indicates that observational evidence,[14] which seemed to show inverse associations of blood pressure with recurrent stroke risk among non-hypertensives, was likely to be the result of confounding, and provides further confirmation of the importance of basing inference about both the direction and size of treatment effects on evidence from randomised trials.[27,28]

The failure of several earlier trials[20] to show convincingly effects of other blood-pressure-lowering regimens on the risk of stroke recurrence seems likely to be the consequence, at least in part, of the smaller reductions in blood pressure achieved and the smaller numbers of participants in those trials. On the basis of the size of the overall blood-pressure difference achieved in PROGRESS (9/4 mm Hg), the observed reduction in stroke risk (28% [SE 3]) was broadly consistent with effects that would be predicted from the results of previous randomised trials of various blood-pressure-lowering regimens in patients with hypertension, in which blood pressure was reduced by 5–6 mm Hg diastolic.[18] By contrast, the observed reduction in major coronary events (26% [SE 9]) seemed to be about twice as large as that which would have been predicted from the results of those earlier trials of mainly diuretic-based and β-blocker-

based regimens,[18] although the confidence interval for the estimate of treatment effect in PROGRESS was wide. This reduction in, mainly initial, coronary events with a regimen involving both an ACE inhibitor and a diuretic was, however, of similar size to the one-fifth reduction in, mainly recurrent, coronary events seen in the Heart Outcomes Prevention Evaluation (HOPE) Study[29] and other major trials[19,30] of ACE inhibitors.

Similarly, the overall reduction in recurrent stroke risk seen in PROGRESS was of comparable size to the reduction in, mainly initial, stroke risk seen in the HOPE Study (32% [SE 9]).[29] Both these studies have now shown clear benefits of treatment for high-risk, non-hypertensive individuals as well as for those with hypertension. However, the large reductions in stroke risk seen in these two trials contrast with the results of earlier large trials of various ACE inhibitors (including ramipril, the agent used in HOPE) among patients with heart failure or left-ventricular dysfunction, in which there was no clear reduction in stroke risk (4% [SE 9]).[30] The results of those earlier trials are broadly consistent with the results seen in PROGRESS for participants who received single-drug therapy with perindopril alone. It is possible that the apparent discrepancy between trials in the size of the effects of ACE inhibitors on stroke risk is the result of chance, since the results of all trials are consistent with a true reduction in risk of between a sixth and a fifth among patients given single-drug therapy with any of these agents.

Prespecified subgroup analyses showed marked heterogeneity of treatment-effect size for stroke risk between participants who received combination therapy with perindopril plus indapamide and those who received single-drug therapy with perindopril alone. Combination therapy reduced blood pressure by 12/5 mm Hg and reduced stroke risk by about two-fifths, with similar benefits in hypertensive and non-hypertensive participants. By contrast, single-drug therapy reduced blood pressure by 5/3 mm Hg with no discernible effect on stroke risk, although the confidence interval was wide and consistent with the moderate effects that would be predicted for the blood-pressure reduction achieved (ie, a one-fifth to one-sixth reduction in stroke risk[17]). For total major vascular events, there was similar evidence of heterogeneity of treatment effect sizes. Although participants were not randomised between combination and single-drug therapy, differences in the characteristics of those who received one drug or two were slight and adjustment for these did not diminish the strength of the evidence for heterogeneity or alter the size of the estimates of treatment effect. It seems, therefore, likely that the large differences in the observed effects of combination and single-drug therapy represent real differences in therapeutic efficacy determined by the difference in blood pressure reductions achieved. This assumption is consistent with direct evidence from randomised trials in other groups of patients, which showed that more intensive blood-pressure lowering confers greater reductions in stroke risk.[19]

The absolute risk reductions seen in PROGRESS are large and are likely to be regarded as worthwhile by many patients and their doctors. The results suggest that 5 years' treatment with the combination of perindopril and indapamide would have resulted in the avoidance of one fatal or major non-fatal vascular event among every 11 patients (95% CI 9–16) assigned active treatment. Absolute benefits of this size greatly exceed the estimated absolute benefits of blood-pressure-lowering treatments for most patients with uncomplicated hypertension.[31] They also compare favorably with the absolute benefits of ACE inhibitor therapy for individuals with coronary heart disease,[19,29] and of other established secondary preventive therapies, such as antiplatelet therapy for patients with ischaemic stroke or transient ischaemic attack,[4,5] or cholesterol lowering with statins for patients with a history of myocardial infarction or unstable angina.[32–34]

Given that the study treatment was shown to be safe and effective across a broad range of patients, irrespective of blood pressure, type of qualifying cerebrovascular event, time since last event, or geographic region, the results should have implications for the care of a large proportion of all patients who survive stroke or transient ischaemic attack. For patients presenting with an acute stroke or transient ischaemic attack, the responsible physician should consider starting treatment at the time of discharge from hospital or at a post-discharge follow-up visit. For others who have had a stroke or transient ischaemic attack in the past, the general practitioner should consider starting treatment at the patient's next visit to the surgery. Although treatment may commence with a single agent, as it did during the run-in phase of this study, the objective should be to move patients onto combination therapy as soon as possible.

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